PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015; **24**: 276–285
Published online 4 February 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3741

ORIGINAL REPORT

Treatment with rivastigmine or galantamine and risk of urinary incontinence: results from a Dutch database study†

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ABSTRACT

Background Treatment of Alzheimer disease (AD) with cholinesterase inhibitors (ChEIs) may increase the risk of urinary incontinence (UI).
Objective To assess whether ChEI use was associated with the risk of UI among older patients with AD.
Methods A crossover cohort study using the PHARMO Record Linkage System included 10 years of data on drug dispensing histories for over two million Dutch residents. Included patients were aged 50 +, free of UI for the last 6 months, received a first ChEI prescription during the study period, had at least 12 months prior drug exposure history and one subsequent prescription of any drug. UI was defined as a first dispensing of a urinary spasmolytic or of incontinence products for at least 30 days. Cox regression with time-varying covariates and multivariate adjustment allowed assessing whether UI incidence was associated with ChEI exposure.
Results Among 3154 patients there were 657 UI cases during a mean follow-up of 5.1 years before a first ChEI dispensing, and 499 cases after ChEI initiation, during a mean follow-up of 2.0 years. Among the 2700 participants free of UI one year before ChEI initiation, the adjusted hazard ratio (HR) for UI was 1.13 (95% CI: 0.97–1.32) when periods with ChEI use were compared to periods without ChEI use. Sensitivity analyses may suggest an increased risk in the 1st month after ChEI initiation (HR: 1.72, $p = 0.09$)
Conclusion Worsening AD may increase incidence of UI, but no firm association between ChEI treatment and risk of UI could be shown from these data. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—Alzheimer disease; cholinesterase inhibitors; urinary incontinence; database cohort study; pharmacoepidemiology

Received 21 May 2014; Revised 18 November 2014; Accepted 26 November 2014

BACKGROUND

Current estimates indicate that 35.6 million people worldwide are living with Alzheimer disease (AD) or other forms of dementia; this number will double by 2030.[1] The prevalence of AD increases with age, reaching 30% of the population in western countries by age 80 and over.[2] According to several studies on community dwelling seniors, i.e. persons aged 65 years or more, urinary incontinence (UI) is more common among seniors with AD than among those without this disease.[3,4] UI may be secondary to the development of AD, it may stem from the same underlying disorder, or it may occur concurrently with AD, but as a separate disease.[5] Different types of UI can be distinguished. In AD, a deficiency in cholinergic neurotransmission has been observed, which forms the basis of treatment with ChEIs. This deficiency may also result in functional incontinence due to cognitive disability and decreased motivation.[5] Cholinesterase inhibitors (ChEI) are used in patients with mild, moderate or even severe AD since they increase acetylcholine levels in the brain.[6] To date, they are the only treatment available for persons with AD and related diseases.[7] However, the increase in available acetylcholine may affect cholinergic systems elsewhere than in the brain.[6]

Since muscarinic receptors are important for detrusor contraction in the bladder,[8] anticholinergic

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†Some results in this manuscript have been presented as a poster at the 39th Annual Scientific and Educational Meeting of the Canadian Association on Gerontoloy, December 2–4, 2010 in Montreal, Canada. They were also accepted for an oral presentation at the ICPE 2010 in Brighton, UK, but the presentation had to be withdrawn.

medications are used to treat UI. Although results from randomized controlled clinical trials did not indicate an increased risk of UI with ChEI use,[9,10] a report from Japan found several cases of UI associated with donepezil treatment, suggesting that this ChEI may increase UI risk.[11] A clinical study of 197 AD patients from a US memory clinic showed a significant change towards more incontinence after 26 weeks of treatment with donepezil or rivastigmine.[12] Some case reports on ChEI use in AD patients with Down syndrome also indicated an increased risk of UI associated with ChEI use.[13] Finally, use of ChEIs was associated with a 55% increase in the risk of being prescribed a urinary antispasmodic of anticholinergic character in a population based study using administrative health data.[14] The question therefore remains whether ChEIs may contribute to the development of UI.[12] The frequent co-existence of AD together with continence problems represents an important clinical challenge. These co-occurring diseases may require medications with opposing pharmacological actions, leading clinicians to question the use of anticholinergic medications to treat UI in patients receiving ChEIs, since they may lead to worsening cognition.[5] Indeed, a US study concluded that in higher-functioning nursing home residents, the concomitant use of ChEIs and anticholinergic medications against UI may result in greater rates of functional decline than use of ChEIs alone.[15] Many educated patients and families are also asking why their physician would use one medication to increase cholinergic activity while also using another medication to inhibit the very same system. Outside of clinical studies, the prescription of urinary antispasmodic medication has been used as a proxy for the development of UI.[14] However, since UI is often managed with incontinence products alone, assessing UI by use of urinary antispasmodics may seriously underestimate its incidence.[12] In the Netherlands a complete range of incontinence products, including pads and undergarments, are reimbursed by the health insurance system and its use is thus documented in administrative data. The population-based PHARMO record linkage system (RLS) offered the rare opportunity to study the association between ChEI treatment and incidence of UI by using the dispensing history of both urinary antispasmodics and incontinence products as a measure for UI incidence.

METHODS

Study data

Data for this study were obtained from the PHARMO Record Linkage System (PHARMO RLS), which is a large, dynamic, patient oriented data network designed for use in pharmacoepidemiology and outcome studies (www.pharmo.nl). Longitudinal data in the PHARMO RLS consist of, among other data, drug dispensing records from community (outpatient) pharmacies. [16,17] The PHARMO cohort for this study comprised more than 2 million inhabitants of 25 both rural and urban areas, scattered over the Netherlands. This database has been shown to be representative of the Dutch population.[18] An important advantage of this database is its virtually complete coverage of a relatively homogenous population of reasonable size.[19]

As reported by Sternogachis[19], in the Netherlands medical care including prescription medications is practically paid completely by a universal insurance system of public and private origins. This also results in healthcare of virtually uniform quality being provided to all citizens, regardless of their geographical location in this densely populated country. Since practically all patients in the Netherlands are registered with a single community pharmacy, independent of the prescriber, pharmacy records are virtually complete with regard to prescription medications. For this study, the computerized medication dispensing histories were used. They contain the name, dose and code of the dispensed medication, dispensing date, prescriber, amount dispensed and the prescribed dosage regimen. The duration of use of each dispensed medication was estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Medications are coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification.[20] According to a validation study of medication exposure assessment from these Dutch pharmacy records, the specificity of the assessment was found to be high, ranging between 0.93 and 1.00, depending on the examined medication class and when compared to assessment by home interview.[21] The positive predictive value ranged between 0.84 and 1.00 for important drug categories and the legend time method, whereas sensitivity ranged between 0.67 and 0.91 under the same conditions.[21] Compared to the validity of other prescription databases these results are considered as good overall.[21] Patient information includes sex and date of birth. Each patient is registered with an anonymous unique patient identification code that allows for observation of a patient's medication therapy over time.[21] The database does not provide information concerning the indication for use of the medicine.

DOI: 10.1002/pds

Study sample and follow-up

Since 1998 the cholinesterase inhibitor rivastigmine, and since 2003 galantamine, have been approved for the treatment of mild to moderate AD in the Netherlands—whereas donepezil has never been approved for reasons inherent to the Dutch health care system.[22] All patients from the PHARMO RLS dataset who received at least one dispensing of rivastigmine or galantamine between July 1998 and January 2008 were identified. Patients were included in the study if at initiation of rivastigmine or galantamine they were 50 years or older, had at least one prior year of medication exposure history in PHARMO and at least one subsequent dispensing of any medication. Complete follow-up as available in PHARMO for all ChEI users was used to calculate background incidence, i.e. incidence during the years leading up to ChEI initiation. All patients were diagnosed with AD preceding the prescription of a ChEI. AD generally develops in a slow process stretching over a period which may last for more than a decade.[23] To take changes in morbidity status regarding AD into account, the incidence density of UI was calculated for four different time periods, i.e. (i) the period starting with the patient's entry into the study until initiation of ChEIs (background incidence), (ii) the period of the last 365 days before initiation of ChEIs, (iii) periods during ChEI use and (iv) periods after ChEI use.

However, for all analyses on the association between ChEI use and UI incidence, cohort entry was limited to 365 days before a first ChEI dispensing. This shortened follow-up entailed limiting the study sample to patients free of UI at 365 days before ChEI initiation. Since, according to Dutch treatment guidelines, ChEIs can only be initiated in patients with clinically confirmed mild to moderate AD, and AD has a slow development, similar disease status can be assumed among patients in the last year leading up to ChEI initiation. The shortened follow-up was chosen to ensure a more comparable disease status among patients and to limit the effect of change in disease status and other characteristics during follow-up. Participants were followed until incidence of UI treatment, loss to follow-up or end of follow-up, whichever event came first (please refer to Figure 1). All information on ChEI exposure and confounders, including co-medication, was censored at the end of follow-up for each subject, so that for subjects experiencing UI before ChEI initiation no ChEI exposure time was considered. In agreement with prior research, after

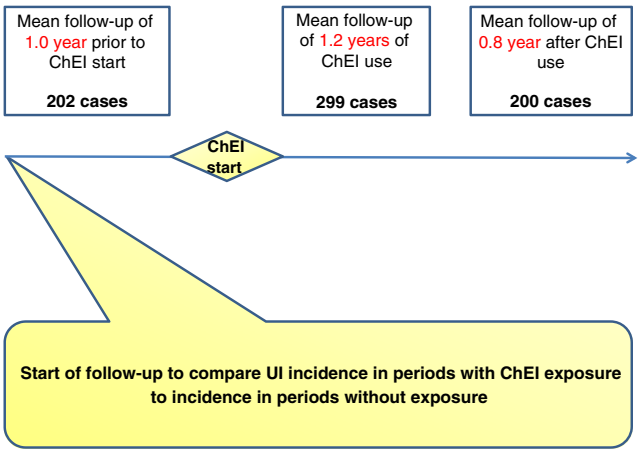

Figure 1. Follow-up of 2700 ChEI users in PHARMO, 1998–2008

12 months only about 40% of patients of this study continued ChEI treatment, suggesting a rather similar development of disease status among ChEI users in this sample.[24]

Outcome

UI incidence was measured by incidence of UI treatment and defined as either a first dispensing of any medication of the ATC group G04BD[20], which were found in these data, i.e. flavoxate (G04BD02), oxybutynin (G04BD04), tolterodine (G04BD07), solifenacin (G04BD08) or darifenacin (G04BD10), or the initial dispensing of at least 30 units of incontinence products within a 90-day period. In the Netherlands, a diagnosis of incontinence may lead to a GP's prescription of antispasmodics or of incontinence products, which will then both be reimbursed by the insurance system. Therefore, a complete range of incontinence products, including pads and undergarments, are distributed by the pharmacies which will then bill these products to the health insurance system so that the PHARMO prescription data comprise data on dispensing of these products. Although it cannot be excluded that patients also purchased incontinence products elsewhere it is quite unlikely they would not take advantage of the reimbursed products: a month supply of incontinence undergarments or pads was considered a proxy for a diagnosis of incontinence in this study. Use of an urinary antispasmodic or incontinence products during the last six months before start of follow-up within the PHARMO cohort, i.e. well before initiation of ChEI use, was considered as a prevalent case of UI: prevalent cases were excluded from all further analyses.

DOI: 10.1002/pds

Exposure to cholinesterase inhibitors

For each cohort member all ChEI dispensings were identified. No use of ChEI patches was reported in this study sample between 1998 and 2008. Dosing instructions and the number of dispensed medication units permitted calculating the prescribed treatment duration. Patients were considered exposed to a ChEI on all dates for which, according to the prescription, medication was dispensed by the pharmacy, i.e. all days within the calculated treatment duration. Treatment episodes were defined as a series of subsequent dispensings. As stated in the Dutch guidelines for the diagnosis and treatment of dementia from 2005 among patients aged ≥50 years, dementia is practically the only diagnosis leading to treatment with ChEIs.[25] Moreover, Dutch guidelines state that ChEIs can only be prescribed for patients with probable or possible AD. Up to 2008, i.e. for 10 out of 11 years of the study period, the prescriber was required to provide a formal statement to the insurance company indicating that the patient was suffering from AD in order for ChEIs to be reimbursed. A Mini-Mental State Examination score compatible with a diagnosis of mild or moderate AD also had to be provided. There may have been some off-label use, but given the strict guidelines we expect such use to have been unimportant. Since 2008, rivastigmine could be prescribed for Parkinson disease dementia and Lewy body dementia. However, given the Dutch guidelines and restrictions on prescribers, it is likely that the vast majority of patients in this study had mild-to-moderate AD dementia.

Recent US and Dutch guidelines recommend dosages of 6–12 mg/day for rivastigmine and 16–24 mg/day for galantamine as clinically beneficial.[25,26] As shown in previous research, in this population the median dose of the last dispensing of rivastigmine was 6 mg (IQR 3–9) for all study patients.[24] For galantamine, the median dose of the last dispensing was 16 mg (IQR 16–24) for all patients and 24 mg (IQR 16–24) for those persisting after 6 months.[24] Given that ChEIs were mostly dosed according to recent treatment guidelines, data on dosing was not specifically included in the present analyses. However, to account for low dose titration at treatment initiation, for persistence of medication in the blood after treatment discontinuation, and for problems with treatment adherence, the gap between the end date of the previous treatment and the date of the following dispensing, within the same treatment episode, was allowed to be a maximum of 30 days, regardless of switching from one type of ChEI to another. All other times were considered unexposed to ChEIs. All treatment episodes were taken into account in this study. A time-dependent variable for exposure was defined to assess the association between ChEI treatment and UI: at each date during follow-up each patient was either exposed to a ChEI or not (please refer to Figure 2).[27]

Potential confounders

Among patients included in the sample for analyses on the association between ChEI use and UI, those who developed UI were compared to those who did not, regarding age, proportion of women, chronic disease score (CDS), type of ChEI used and treatment with a medication against benign prostatic hyperplasia (BPH), as indicated by use of alfuzosin (G04CA01), finasteride (G04CB01), dutasteride (G04CB02), terazosin (G04CA03), tamsulosin (G04CA02) or prostate cancer surgery, indicated by the use of flutamide (L02BB01), bicalutamide (L02BB03) or nilutamide (L02BB02) and use of antipsychotics. The CDS is a validated, prognostic measure of co-morbidity, higher scores indicating greater chronic disease burden. The CDS is based on a patient's medication profile as derived from prescription data for a 12-month period; the score is treated as a continuous variable in analyses and has been used in a ChEI discontinuation study of this population.[24,28] These characteristics were used to adjust analyses on associations between ChEIs and UI, together with a large number of other co-medications, which may be associated with UI: the above mentioned medications against BPH, anticholinergic medications (gastrointestinal anticholinergics, antiepileptics, tricyclic antidepressants or antihistimines; ATC codes A03, N03A, R06AA, RB, R06AC, R06AD and N06AA),

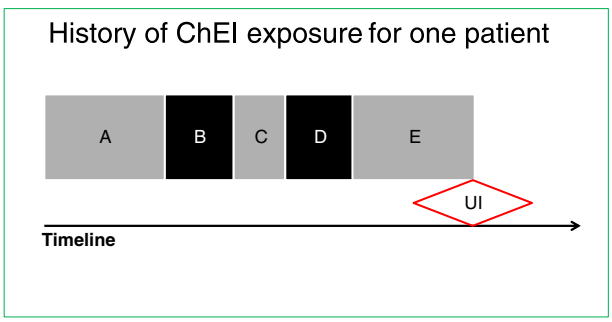

Figure 2. History of ChEI exposure for one patient

DOI: 10.1002/pds

cardiac medications (beta blockers, calcium channel blockers, statins, angiotension-converting-enzyme inhibitors and Angiotensin II inhibitors), analgetics, prokinetics, benzodiazepines, diuretics, Parkinson medications, antipsychotics, selective serotonin reuptake inhibitors (SSRIs) or other antidepressants.[14,29] Since use of comedications may change during follow-up, for each period of a treatment episode, as well as for periods without ChEI exposure, it was determined whether a patient had at least one active dispensing for one of the co-medications: he was either exposed or unexposed to the co-medication for that period. Since patients were censored after UI incidence, subsequent periods of ChEI or co-medication exposure were also censored.

In conclusion, periods of exposure to ChEIs were constructed from dispensing data, allowing a gap of 30 days between the end of a prescription and the start of the subsequent prescription. All data on use of other medications which might confound the association between ChEIs and UI were used in a time-dependent manner with regard to the ChEI exposure periods: if a patient had obtained a dispensing for one of the comedications during a period of ChEI exposure or during an unexposed period, he was considered exposed to the comedication for that period. The covariates age, gender and CDS, however, were determined at baseline only and used without further time dependency.

Study design and data analyses

AD patients who receive ChEI treatment may differ from those without such treatment for several characteristics, which may confound associations. Therefore a crossover cohort design was chosen for this study, so that every patient was exposed to ChEIs at some time during follow-up but unexposed at other times. In this design every patient serves as his own control, limiting confounding for patient characteristics that do not vary during follow-up.[30] The crossover cohort design is an extension of the case-crossover-design, which was initially developed for studies in which the exposure is intermittent, the effect on risk immediate and transient, and the outcome abrupt.[31] However, there is no sharp conceptual line between case-crossover and crossover cohort studies,[30] and in the last decade, the crossover design has been used to study single changes in exposure level and outcomes with insidious onsets. The present analyses built on this understanding, on Petri's prescription sequence symmetry analyses[32] used for a study on antidepressant use and urinary incontinence based on PHARMO data, [29] and on previous applications of this design to health data.[30,33] In short, incidence density for exposed cases, that is those who used the hypothesized causal medication (i.e. ChEIs) when the hypothesized outcome (i.e. incidence of UI) happened, was expected to be greater than for unexposed cases, that is those with the opposite sequence of events. Controls contribute person-time to exposed and unexposed periods but do not experience events. Under these circumstances, the case window is a period of various lengths before the outcome happens, and the control window is a similar period before and after the exposure periods.[30] Thus, the crossover cohort design enabled calculating risk of UI incidence in relation to ChEI exposure duration.

Two types of analyses were performed to examine the associations between ChEI use and UI risk. First, UI incidence densities were calculated for three periods: during the last year before ChEI initiation, as well as during and after ChEI use. Poisson regression with adjustment for age, sex and CDS, was used to calculate incidence density ratios comparing exposed and unexposed periods. For the crossover cohort design analyses, the hazard ratios (HR) and 95% confidence intervals (95% CIs) were calculated using Cox proportional hazard regression to compare UI incidence during the exposed and unexposed periods, comprising one year before ChEI initiation and all periods after ChEI use.[34] Calendar-time was used as time scale, with different exposure periods being defined from the first ChEI initiation date, thus effectively accounting for the year of ChEI initiation (between 1998 and 2007) in building the models. Three regression models with time-dependent exposure variables were computed: unadjusted, adjusted for age, gender and CDS, and adjusted for age, gender, CDS and concurrent co-medications. The effect of treatment type, i.e. rivastigmine versus galantamine, was examined in sub-group analyses, performed with adjustment for the same confounders as in the previous models. Modification of risk ratios for UI by ChEI type was formally tested within the Cox regression model comprising exposure to ChEI at the time of UI onset and adjustment for sex and CDS using interaction terms. We also performed sensitivity analyses to assess whether results differed according to the proxy used to measure UI, i.e. for patients using urinary antispasmodics as compared to those using incontinence products. Further sensitivity analyses investigated whether limiting follow-up to respectively one, three, six months before and one, three,

DOI: 10.1002/pds

six or twelve months after initiation of ChEIs might reflect a more appropriate time-window for the observation of an increased risk of UI incidence, shortly after ChEI initiation.

RESULTS

There were 3358 patients with a first dispensing of rivastigmine or galantamine between January 1998 and December 2007. All of these had at least one year of follow-up within the database before ChEI initiation. Among them, 204 were excluded since urinary antispasmodics or incontinence products were dispensed within the first 6 months of their entry into the database, and thus may have been dispensed for prevalent UI. Consequently, the first 6 months of follow-up were excluded from the analyses for all subjects to prevent immortal time bias.

Among the remaining 3154 subjects, 657 cases of incident UI were observed during the complete follow-up before initiation of ChEIs (5.1 years), for an incidence density (ID) of 40.98 cases/1000 person-years (py). From beginning of follow-up to the last 365 days before ChEI initiation (4.23 years), there were 455 UI cases, for an ID of 34.1/1000 py, and within the last 365 days preceding ChEI initiation, there were 202 cases, for an ID of 77.39/1000 py. There were 299 UI cases observed after initiation of ChEIs and during ChEI use (1.17 years), for an ID of 102.68/1000 py, and finally 200 UI cases were observed in periods after ChEI use (0.81 year), for an incidence density of 98.77/1000 py.

Since follow-up for analyses on the association between ChEI use and UI was limited to subjects free of UI at 365 days before ChEI initiation, the 454 patients who experienced UI incidence until 365 days before ChEI initiation were excluded from the analyses, leaving 2700 subjects for further analyses (please refer to the flow-chart in Figure 3). Table 1 shows the distribution of several characteristics among these subjects, separately for those who developed UI and for those who stayed continent. UI cases were a little older at study entry, had a higher chronic disease score, comprised fewer women, were more likely to use rivastigmine than galantamine, were more likely to receive medication against benign prostatic hyperplasia or prostate cancer and more likely to receive antipsychotics than subjects staying continent. These characteristics were used to adjust regression analyses on the association between ChEI use and UI incidence. Among all 702 UI cases occurring from 365 days before ChEI initiation to the end of follow-up, 108 (15.4%) were identified by use of urinary antispasmodic medication, 593 (84.5%) by use of incontinence products and 1 (0.1%) by use of both. Cox regression analyses allowed considering time-dependent exposure to ChEIs and adjustment for co-medications in a time-dependent manner. Results showed no significantly increased risk of UI when unexposed periods during the 365 days before ChEI initiation combined with periods after ChEI use were compared to exposed periods: the adjusted hazard ratio (HR) was 1.13 with $p = 0.12$ (please refer to Table 2). These results are similar among subjects on rivastigmine (HR = 1.13, $p = 0.15$) and those on galantamine (HR = 1.10, $p = 0.55$) in adjusted models. Among the 108 subjects for whom UI was identified via use of urinary antispasmodics, the adjusted HR for UI during follow-up was 1.22 (95% CI: 0.82–1.81), whereas it was 1.12 (95% CI: 0.95–1.32) among those for whom UI incidence was assessed

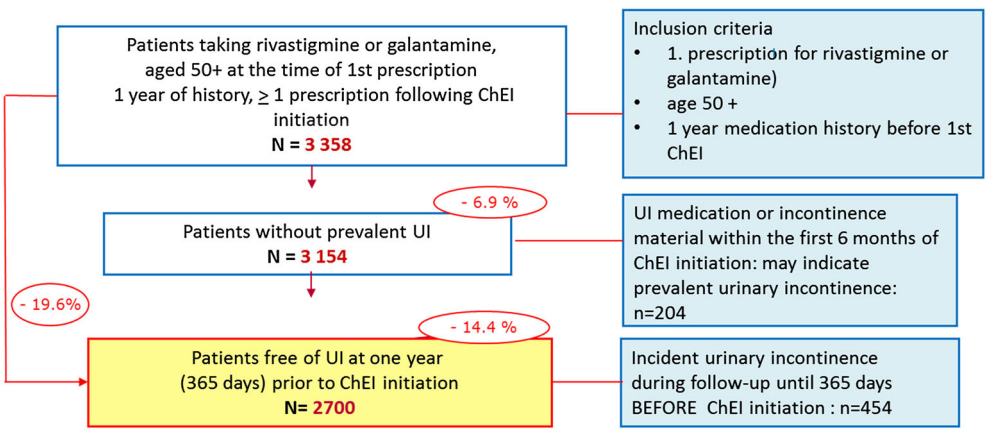

Figure 3. Flow-chart for study sample

DOI: 10.1002/pds

Table 1. Characteristics among 2700 subjects treated with cholinesterase inhibitors (ChEIs), according to the development of urinary incontinence (UI)

Characteristic*	Complete sample ($n = 2700$)	Stayed continent during follow-up ($n = 1998$)	UI cases (before, during or after ChEI use) ($n = 702$)	p-value[†]
Age at study entry*, mean, y, (SD)	75.7 (7.7)	75.6 (7.8)	76.0 (7.3)	0.033
Chronic disease score, mean, (SD)	3.42 (2.86)	3.32 (2.76)	3.70 (3.10)	<0.001
Sex, % (n) women	50.8 (1371)	51.9 (1037)	47.6 (334)	0.049
Type of dementia medication, % (n)				
• Rivastigmine	61.4 (1657)	56.9 (1137)	74.1 (520)	<0.001
• Galantamine	31.4 (847)	35.6 (712)	19.2 (135)	
•Switching between the two	7.3 (196)	7.5 (149)	6.7 (47)	
On BPH or prostate cancer medication, % (n)[‡]	6.2 (167)	5.7 (113)	7.7 (54)	0.054
Use of antipsychotics, % (n)[§]	14.5 (392)	13.6 (271)	17.2 (121)	0.018

*For this comparison, study entry is 365 days before start of ChEI treatment.
[†]The p-values were obtained from Chi square test or Student t-tests as appropriate.
[‡]"Use of any medication against BPH or prostate cancer" comprises alfuzosin, tamsulosin, terazosin, finasteride, dutasteride, flutamide, nilutamide and bicalutamide (G04CA01, G04CB01, G04CB02, G04CA03, G04CA02, L02BB01, L02BB03, L02BB02
[§]"Use of antipsychotics" comprises the medications with the ATC codes N05AA, N05AB, N05AC, N05AH02 and N05AH03.

Table 2. Hazard ratios (HR) from Cox proportional hazards regression analyses for the association between exposure to ChEI treatment and incident urinary incontinence (UI)

Adjustment	UI cases/censored	HR for exposure to ChEIs at the onset of UI	95% CI
Among all subjects free of UI one year before ChEI start ($n = 2700$)			
Unadjusted model	702/1998	1.11	0.95–1.29
Adjusted for age, sex and CDS		1.15	0.98–1.34
Fully adjusted[†]		1.13	0.97–1.32
Among subjects on rivastigmine*, free of UI one year before ChEI start ($n = 1853$)			
Unadjusted model	566/1287	1.12	0.94–1.32
Adjusted for age, sex and CDS		1.14	0.96–1.35
Fully adjusted		1.13	0.95–1.34
Among subjects on galantamine*, free of UI one year before ChEI start ($n = 1043$)			
Unadjusted model	182/861	1.03	0.76–1.40
Adjusted for age, sex and CDS		1.12	0.83–1.51
Fully adjusted		1.10	0.81–1.50

*Included subjects may have switched between rivastigmine and galantamine during follow-up.
CDS: chronic disease score.
[†]The models were adjusted for ChEI type and the following co-medications: prostate medications: anticholinergics (A03, N03A, R06AA, R06AB, R06AC, R06AD and N06AA, but excluding antipsychotics (N05AA, N05AB, N05AC, N05AH02 and N05AH03)), SSRIs, H2-receptor antagonists, prokinetics, benzodiazepines, diuretics, Parkinson medications, non tricyclic antidepressants and all antipsychotics.

via use of incontinence products. Several sensitivity analyses have been performed to compare reduced time-windows of exposure, i.e. one, three, six or 12 months before and after ChEI initiation. Results comparing incidence risk between, respectively, the last three months or the last six before initiation with the first three or six months after initiation, changed these results only minimally: HRs were close to one and no statistically significant results were observed. For the comparison of 12 months before ChEI initiation and a follow-up of 12 months after ChEI start the fully adjusted HR was also similar, at 1.23 (95% CI: 0.99–1.51). If risk was compared between the last month before and the first month after ChEI initiation, an increased risk of UI incidence could be observed in the fully adjusted model, with a HR of 1.72 (95% CI: 0.92–3.26), which did, however, not reach significance ($p = 0.09$).

DISCUSSION

An increase in the incidence of UI was observed among the subjects of this study during the five years prior to initiation of ChEIs as an AD treatment and also following ChEI initiation. However this increase was not significantly associated with exposure to ChEIs, when the periods of one year before and the time after ChEI use were compared to exposed periods, after adjustment for age, gender, chronic disease score and a large number of co-medications in Cox regression models. Restraining the follow-up to the last month before and the first month after ChEI initiation showed a 70% increased risk which did not quite reach statistical significance.

Strengths of this study

Reimbursement of incontinence products in the Netherlands enabled including their use as a proxy

DOI: 10.1002/pds

measure of UI incidence, which is not possible in health administrative data from most countries: 84.5 % of the UI cases in this study were assessed by the use of such material. A large number of co-medications were included in the adjustment of regression models in a time-dependent fashion. Finally, although no information on AD severity was available in the administrative data, Dutch physicians had to strictly follow guidelines allowing them to prescribe ChEIs only to patients with mild to moderate disease, as confirmed by cognitive testing.[25]

Study limitations

Several limitations apply to this study. Left censoring, due to leaving PHARMO because of death or nursing home placement, may have prevented assessment of some UI cases. Moving from a normal residence to a care facility which was not a nursing home, however, would not have resulted in leaving PHARMO. The database did not provide information on differential diagnosis or severity of AD However, among subjects aged 50 years or more in the Netherlands, dementia, including AD, Parkinson's disease dementia and Lewy Body dementia, are the only diagnoses leading to ChEI treatment.[25] Also use of antipsychotics may be regarded as a proxy for worsening AD[35] and results were adjusted for these medications. Immortal time bias is considered as absent from this study, since for all subjects included in the Cox regression both exposure to ChEIs and UI were assessed from the beginning of follow-up, until either the incidence of an event, loss to follow-up or end of study, whichever came first. Also, theoretical durations for dispensed medications, as calculated from dosing instructions and dispensed quantities, may not always reflect medication related behavior by patients. We therefore allowed for a 30-day period after the theoretical end of a prescription and considered this period as exposed, similarly as in other studies on ChEI use on the same population.[24,33] Nevertheless, one has to bear in mind that health administrative data do not permit to truly evaluate medication adherence because the possibility remains that patients acquire medications, or persist with treatment, without using them as indicated.[36] There was a marked increase in UI incidence density when the period of five years to one year before ChEI start was compared to the last year before ChEI start, and further to the time after ChEI start. It might be possible that processes leading from subtle cognitive impairment to memory problems and then to diagnosed AD may also lead to an increase in UI,[5] as does increasing age.[37] Results from Poisson regression with basic adjustment show significant IDRs for an increased risk for UI during periods of ChEI exposure, as compared to the year before and the periods after ChEI use. However, HRs from Cox regression were not significant for this association. This may be explained by the time-dependent assessment of risk in Cox regression. The 70% increased risk of UI during the first month after ChEI initiation, as compared to the last month before treatment with this medication, albeit not statistically significant, may suggest that patients who experience UI following ChEI initiation do so shortly after treatment start and that some of them may indeed stop the treatment for this reason: in this cohort 8.5% of patients discontinued ChEIs after one month.[24] When follow-up was prolonged, this possibility of an increased risk could not be observed anymore. Using the present data it is impossible to distinguish whether any increase in UI incidence following ChEI initiation was related to worsening of dementia, effects of ChEIs leading to urinary outflow obstruction[38] or both.

The present results are in agreement with a review stating the relative paucity of case reports and with the absence of evidence of increase of UI in controlled clinical trials on ChEIs, which may suggest that these do not pose an important risk of UI.[39] Since this review, few observational studies reported on the association between UI risk and use of ChEIs. A study from Canada observed a HR of 1.55 (95% CI: 1.39–1.72) for the association of UI with ChEI use in a retrospective cohort study using administrative data of 44 884 dementia patients, including 20 491 ChEI users, but UI was defined by use of urinary antispasmodics only. Case selection was therefore likely different from the present study.[14] Starr *et al.* found an odds' ratio of 2.91 (95% CI: 1.06–7.99) for the association of UI with use of rivastigmine in a population-based retrospective study of 197 fully continent patients of a memory treatment center with a mean age of 76.7 years.[12] This study observed that in half a year (over 6 months) 6.6% of patients lost full continence, which is a larger loss of continence than observed in the present study, where the adjusted yearly UI incidence density varied between 7.7% and 10.3%. However, Starr *et al.* also observed significant associations between worse continence and cognitive and behavioral decline, implying that in patients responding to ChEIs improved cognition and behavior offset the potential for worse continence. Finally, their patients were slightly older than those in our study and might have been sicker. It is also of note that the Netherlands are the European country which has the lowest prevalence of ChEI use.[40] A comparatively

DOI: 10.1002/pds

sparing use of these agents may explain that associations between ChEI exposure and UI incidence in the Netherlands were different from associations observed in Canada or elsewhere.[14]

CONCLUSION

The present study did not show a significantly increased risk of UI during the first three, six or twelve months or during prolonged periods of exposure to ChEIs, as compared to periods of comparative lengths in the year before or in the time after ChEI use, in a population-based sample of community dwelling seniors, and based on an assessment of UI by use of UI medication or incontinence products. Since an increased risk was observed for the first month after ChEI initiation, albeit at the limit of statistical significance, and since UI is a frequent, multi-factorial problem among frail seniors with a negative impact on their quality of life, randomized controlled trials on cholinesterase treatment in patients with both AD and risk of UI should be performed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Alzheimer's disease is a devastating progressive neurological disorder, eventually leading to nursing home placement for most patients. Urinary incontinence is a condition often complicating Alzheimer's disease and contributing to nursing home placement.
- Cholinesterase inhibitors (ChEI) are the only medications used to decrease disease symptoms in mild or moderate disease and to delay progression to severe stages. They act by increasing acetylcholine, which may in turn contribute to urinary incontinence (UI).
- Limited evidence exists about the risk of increased UI with use of ChEIs and patients, caregivers or health care professionals may fear an increased risk of UI with ChEI use.
- In the Netherlands urinary spasmolytics and incontinence products are both reimbursed by the health insurance system and their use is documented in administrative data. The analysis of data about rivastigmine or galantamine use from 3358 Dutch patients, during several years of follow-up, did not show evidence of an increased risk of UI following prolonged use of one of these medications.

ETHICS STATEMENT

Pharmacoepidemiological studies on data from PHARMO-RLS do not include any information allowing the identification of individual persons but uses data collected anonymously. According to current Dutch law no ethical approval for this study was required. Also, community pharmacists who do provide their dispensing data to PHARMO RLS have to inform their patients about the fact that their anonymous patient data from the pharmacy may be used for research purposes.

ACKNOWLEDGEMENTS

This study received financial support from the Canadian Institutes for Health Research (CIHR) (research fellowship for EK), from the Division of Pharmacoepidemiology and Pharmacotherapy at Utrecht University (UIPS) and the Centre d'excellence sur le vieillissement de Québec (CEVQ), Québec, Canada. The division of Pharmacoepidemiology and Pharmacotherapy at Utrecht University, which employs TE and PS, has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl, which includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board and the Dutch Ministry of Health. The CIHR, UIPS or CEVQ were not involved in the study design, conduct or analyses, or in the preparation of the manuscript.

All authors of this study have been named and none of them has conflicts of interest that are directly relevant to the content of this study. Authors contributions are as follows: EK was responsible for performing all steps of the study and writing all versions of the manuscript. RvM, PS and TE participated with EK in the study concept, interpretation and discussion of results and read the final version of the manuscript. PS and PHC participated in data analyses and interpretation of results and PHC read the final version of the manuscript. TE procured the data and initiated the study.

REFERENCES

1. World Health Organization. Dementia—A Public Health Priority. Geneva, 2012.
2. Ferri CP, Prince M, Brayne C, *et al.* Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; **366**: 2112–7.
3. Ouslander JG, Zarit SH, Orr NK, Muira SA. Incontinence among elderly community-dwelling dementia patients. Characteristics, management, and impact on caregivers. *J Am Geriatr Soc* 1990; **38**: 440–5.
4. Skelly J, Flint AJ. Urinary incontinence associated with dementia. *J Am Geriatr Soc* 1995; **43**: 286–94.
5. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M. Dementia and lower urinary dysfunction: with a reference to anticholinergic use in elderly population. *Int J Urol* 2008; **15**: 778–88.

6. Wilkinson DG, Francis PT, Schwam E, Payne-Parrish J. Cholinesterase inhibitors used in the treatment of Alzheimer's disease: the relationship between pharmacological effects and clinical efficacy. *Drugs Aging* 2004; **21**: 453–78.
7. Fillit HM, Doody RS, Binaso K, *et al*. Recommendations for best practices in the treatment of Alzheimer's disease in managed care. *Am J Geriatr Pharmacother* 2006; **4**(Suppl A): S9–S24; quiz S5-S8.
8. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. *Physiol Rev* 2004; **84**: 935–86.
9. Rogers SL, Doody RS, Mohs RC, Friedhoff LT. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. *Donepezil Study Group Arch Intern Med* 1998; **158**: 1021–31.
10. Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* 2000; **54**: 2261–8.
11. Hashimoto M, Imamura T, Tanimukai S, Kazui H, Mori E. Urinary incontinence: an unrecognised adverse effect with donepezil. *Lancet* 2000; **356**: 568.
12. Starr JM. Cholinesterase inhibitor treatment and urinary incontinence in Alzheimer's disease. *J Am Geriatr Soc* 2007; **55**: 800–1.
13. Hemingway-Eltomey JM, Lerner AJ. Adverse effects of donepezil in treating Alzheimer's disease associated with Down's syndrome. *Am J Psychiatry* 1999; **156**: 1470.
14. Gill SS, Mamdani M, Naglie G, *et al.* A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med* 2005; **165**: 808–13.
15. Sink KM, Thomas J, 3rd, Xu H, Craig B, Kritchevsky S, Sands LP. Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. *J Am Geriatr Soc* 2008; **56**: 847–53.
16. Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. *J Epidemiol Community Health* 1992; **46**: 136–40.
17. Stricker BH, Herings RM, Bakker A, Valkenburg HA, Sturmans F. Pharmaco-morbidity linking: a potential instrument for post-marketing surveillance. *Ned Tijdschr Geneeskd* 1990; **134**: 1886–9.
18. van der Klauw MM, Stricker BH, Herings RM, Cost WS, Valkenburg HA, Wilson JH. A population based case-cohort study of drug-induced anaphylaxis. *Br J Clin Pharmacol* 1993; **35**: 400–8.
19. Stergachis A, Saunders KW, Davis RL, *et al*. Examples of Automated Databases. In Textbook of Pharmacoepidemiology, Kimmel S, Strom B (eds.). John Wiley & Sons, Ltd.: West Sussex, England, 2006.
20. World Health Organization. WHO Collaborating Center for Drug Statistics Methodology, 2009.
21. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol* 1997; **50**: 619–25.
22. Georges J. The availbility of antidementia drugs in Europe. *Eur Neurol Dis* 2007; **1**: 40–4.
23. Nelson L, Tanner C, Van Den Eeden S, McGuire V (eds). Neuroepidemiology: From Principles to Practice. Oxford University Press: Oxford, 2004.
24. Kröger E, van Marum R, Souverein P, Egberts T. Discontinuation of cholinesterase inhibitor treatment and determinants thereof in the Netherlands: a retrospective cohort study. *Drugs Aging* 2010; **27**: 663–75.
25. Nederlandse Vereniging voor Klinische Geriatrie. Richtlijn Diagnostiek en medicamenteuze behandeling van dementie. Van Zuiden Communicaties B.V.: Alphen a/d Rijn, 2005; 86–7.
26. Qaseem A, Snow V, Cross JT, Jr, *et al.* Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2008; **148**: 370–8.
27. Abrahamowicz M, Bartlett G, Tamblyn R, du Berger R. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. *J Clin Epidemiol* 2006; **59**: 393–403.
28. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol* 1992; **45**: 197–203.
29. Movig KL, Leufkens HG, Belitser SV, Lenderink AW, Egberts AC. Selective serotonin reuptake inhibitor-induced urinary incontinence. *Pharmacoepidemiol Drug Saf* 2002; **11**: 271–9.
30. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health* 2000; **21**: 193–221.
31. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991; **133**: 144–53.
32. Petri H, Leufkens H, Naus J, Silkens R, van Hessen P, Urquhart J. Rapid method for estimating the risk of acutely controversial side effects of prescription drugs. *J Clin Epidemiol* 1990; **43**: 433–9.
33. Kröger E, Berkers M, Carmichael PH, Souverein P, van Marum R, Egberts T. Use of rivastigmine or galantamine and risk of adverse cardiac events: a database study from the Netherlands. *Am J Geriatr Pharmacother* 2012; **10**: 373–80.
34. Allison P. Survival Analysis Using SAS: A Practical Guide. SAS Press: Cary, North Carolina, 1995.
35. Burghaus L, Eggers C, Timmermann L, Fink GR, Diederich NJ. Hallucinations in neurodegenerative diseases. *CNS Neurosci Ther* 2011; **16**: 1755–5949.
36. Cramer JA, Roy A, Burrell A, *et al.* Medication compliance and persistence: terminology and definitions. *Value Health* 2008; **11**: 44–7.
37. Dubeau CE, Simon SE, Morris JN. The effect of urinary incontinence on quality of life in older nursing home residents. *J Am Geriatr Soc* 2006; **54**: 1325–33.
38. Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia: recommendations for family physicians. *Can Fam Physician - Medecin de famille canadien* 2014; **60**: 433–8.
39. Siegler EL, Reidenberg M. Treatment of urinary incontinence with anticholinergics in patients taking cholinesterase inhibitors for dementia. *Clin Pharmacol Ther* 2004; **75**: 484–8.
40. Pariente A, Helmer C, Merliere Y, Moore N, Fourrier-Reglat A, Dartigues JF. Prevalence of cholinesterase inhibitors in subjects with dementia in Europe. *Pharmacoepidemiol Drug Saf* 2008; **17**: 655–60.

DOI: 10.1002/pds